

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1. (currently amended) A method for degrading a transcription factor of a glucose metabolism-related gene, wherein the method comprises making calpain coexist with the transcription factor ~~of the glucose metabolism-related gene~~ in the presence of calcium.
- 2-94. (canceled)
95. (new) The method according to claim 1, wherein calpain is m-calpain and/or  $\mu$ -calpain.
96. (new) The method according to claim 1, wherein the transcription factor of the glucose metabolism-related gene is at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1.
97. (new) An agent capable of degrading a transcription factor of a glucose metabolism-related gene, containing an effective dose of calpain as an active ingredient.
98. (new) The agent according to claim 97, wherein calpain is m-calpain and/or  $\mu$ -calpain.
99. (new) The agent according to claim 97, wherein the transcription factor of the glucose metabolism-related gene is at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1.
100. (new) A method for inhibiting production of a gene product of a glucose metabolism-related gene, wherein the method comprises degrading a transcription factor of the gene by calpain.
101. (new) The method according to claim 100, wherein calpain is m-calpain and/or  $\mu$ -calpain.
102. (new) The method according to claim 100, wherein the transcription factor of the glucose

metabolism-related gene is at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1.

103. (new) The method according to claim 100, wherein the glucose metabolism-related gene is the insulin gene or glucose transporter 2 gene.

104. (new) A method for degrading a transcription factor of a glucose metabolism-related gene, wherein the method comprises changing calcium concentration, and thereby changing the degree of degradation of the transcription factor of the gene.

105. (new) A method for regulating production of a gene product of a glucose metabolism-related gene, wherein the method comprises changing calcium concentration and thereby changing the degree of degradation of a transcription factor of the gene.

106. (new) The method for regulating production of a gene product of a glucose metabolism-related gene according to claim 105, wherein the transcription factor of the glucose metabolism-related gene is at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1.

107. (new) A method for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene, wherein the method comprises inhibiting calpain activity, the cleavage by calpain of the transcription factor, or the binding of calpain to the transcription factor.

108. (new) The method according to claim 107, wherein the method comprises treating a sample or a cell, which is selected from the following group:

- i) an in vitro sample containing at least calpain and the transcription factor,
- ii) a cell that expresses at least calpain and the transcription factor,
- iii) a cell that is carried by a mammal and expresses at least calpain and the transcription factor, and

iv) a pancreatic  $\beta$  cell that is carried by a mammal and expresses at least calpain and the transcription factor, with a substance that inhibits calpain activity.

109. (new) The method according to claim 108, wherein the substance that inhibits calpain activity is at least one member selected from the group consisting of an antibody that recognizes the transcription factor of the glucose metabolism-related gene, and a calpain inhibitor.

110. (new) The method according to claim 109, wherein the calpain inhibitor is at least one member selected from the group consisting of N-Acetyl-Leu-Leu-Met-CHO, N-Acetyl-Leu-Leu-Nle-CHO, Z-Leu-Leu-Tyr-CH<sub>2</sub>F, Mu-Val-HPh-CH<sub>2</sub>F, 4-fluorophenylsulfonyl-Val-Leu-CHO, Leu-Leu-Phe-CH<sub>2</sub>Cl and Z-Val-Phe-CHO.

111. (new) The method according to claim 108, wherein the substance that inhibits calpain activity is a peptide containing at least one amino acid sequence of a calpain-recognized cleavage site in the transcription factor of the glucose metabolism-related gene.

112. (new) The method according to claim 108, wherein the substance that inhibits calpain activity is a peptide that comprises three or more consecutive amino acid residues from the amino acid sequence set forth in any of SEQ ID NOS: 1 to 3 in the sequence listing and contains at least one amino acid sequence of a calpain-recognized cleavage site in the transcription factor of the glucose metabolism-related gene.

113. (new) The method according to claim 112, wherein the calpain-recognized cleavage site in the transcription factor of the glucose metabolism-related gene is selected from the group consisting of Leu-Tyr, Leu-Met, Leu-Arg, Val-Tyr, Val-Met and Val-Arg.

114. (new) The method according to claim 107, wherein calpain is m-calpain and/or  $\mu$ -calpain.

115. (new) The method according to claim 107, wherein the transcription factor is at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1.

116. (new) An agent for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene, wherein the agent inhibits calpain activity, the cleavage by calpain of the transcription factor, or the binding of calpain to the transcription factor.

117. (new) The agent according to claim 116, wherein the agent contains an effective dose of a substance that inhibits calpain activity as an active ingredient.

118. (new) The agent according to claim 117, wherein the substance that inhibits calpain activity is at least one member selected from the group consisting of an antibody that recognizes calpain, an antibody that recognizes the transcription factor of the glucose metabolism-related gene, and a calpain inhibitor.

119. (new) The agent according to claim 118, wherein the calpain inhibitor is at least one member selected from the group consisting of N-Acetyl-Leu-Leu-Met-CHO, N-Acetyl-Leu-Leu-Nle-CHO, Z-Leu-Leu-Tyr-CH<sub>2</sub>F, Mu-Val-HPh-CH<sub>2</sub>F, 4-fluorophenylsulfonyl-Val-Leu-CHO, Leu-Leu-Phe-CH<sub>2</sub>Cl and Z-Val-Phe-CHO.

120. (new) The agent according to claim 117, wherein the substance that inhibits calpain activity is a peptide containing at least one amino acid sequence of a calpain-recognized cleavage site in the transcription factor of the glucose metabolism-related gene.

121. (new) The agent according to claim 117, wherein the substance that inhibits calpain activity is a peptide that comprises three or more consecutive amino acid residues from the amino acid sequence set forth in any of SEQ ID NOS: 1 to 3 in the sequence listing and contains at least one amino acid sequence of a calpain-recognized cleavage site in the transcription factor of the

glucose metabolism-related gene.

122. (new) The agent according to claim 121, wherein the calpain-recognized cleavage site in the transcription factor of the glucose metabolism-related gene is selected from the group consisting of Leu-Tyr, Leu-Met, Leu-Arg, Val-Tyr, Val-Met and Val-Arg.

123. (new) A method for enhancing production of a gene product of a glucose metabolism-related gene, wherein the method comprises inhibiting the degradation of a transcription factor of the gene caused by calpain.

124. (new) The method according to claim 123, wherein calpain is m-calpain and/or  $\mu$ -calpain.

125. (new) The method according to claim 123, wherein the transcription factor of the glucose metabolism-related gene is at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1.

126. (new) The method according to claim 123, wherein the glucose metabolism-related gene is the insulin gene or glucose transporter 2 gene.

127. (new) The method according to claim 123, wherein the method comprises inhibiting the degradation of the transcription factor of the glucose metabolism-related gene by inhibiting calpain activity, by inhibiting the cleavage by calpain of the transcription factor, or by inhibiting the binding of calpain to the transcription factor.

128. (new) The method according to claim 123, wherein the method comprises performing a treatment with an agent for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene, where said agent inhibits calpain activity, the cleavage by calpain of the transcription factor, or the binding of calpain to the transcription factor.

129. (new) An agent capable of enhancing production of a gene product of a glucose metabolism-related gene, wherein the agent contains an effective dose of a substance for

inhibiting the degradation of a transcription factor of the gene, where said substance inhibits calpain activity, the cleavage by calpain of the transcription factor, or the binding of calpain to the transcription factor.

130. (new) A method for preventing and/or treating a disease, comprising inhibiting the degradation of a transcription factor of a glucose metabolism-related gene by inhibiting calpain activity, by inhibiting the cleavage by calpain of the transcription factor, or by inhibiting the binding of calpain to the transcription factor, wherein the disease is selected from the following group:

- i) a disease attributable to the degradation of the transcription factor of the glucose metabolism-related gene,
- ii) a disease attributable to the degradation of at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1,
- iii) a disease attributable to a decrease in a gene product of a glucose metabolism-related gene, and
- iv) a disease attributable to a decrease in a gene product of a gene on which at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1 acts as a transcription factor, and
- v) a disease attributable to a decrease in a gene product of the insulin gene and/or glucose transporter 2 gene.

131. (new) The method according to claim 130, wherein the disease is diabetes.

132. (new) The method according to claim 130, wherein the method comprises performing a treatment with an agent for inhibiting the degradation of a transcription factor of the gene, where

said agent inhibits calpain activity, the cleavage by calpain of the transcription factor, or the binding of calpain to the transcription factor.

133. (new) The method according to claim 130, wherein the disease is liver adenoma or hepatocellular carcinoma, and the transcription factor of the glucose metabolism-related gene is hepatocyte nuclear factor 1  $\alpha$ .

134. (new) The method according to claim 133, wherein the method comprises performing a treatment with an agent for inhibiting the degradation of hepatocyte nuclear factor 1  $\alpha$  (HNF-1 $\alpha$ ), where the agent inhibits the activity of m-calpain and/or  $\mu$ -calpain, the cleavage by m-calpain and/or  $\mu$ -calpain of HNF-1 $\alpha$ , or the binding of m-calpain and/or  $\mu$ -calpain to HNF-1 $\alpha$ .

135. (new) An agent for preventing and/or treating a disease, containing an effective dose of a substance for inhibiting the degradation of a transcription factor of a glucose metabolism-related gene, where said substance inhibits calpain activity, the cleavage by calpain of the transcription factor, or the binding of calpain to the transcription factor, wherein the disease is selected from the following group:

- i) a disease attributable to the degradation of the transcription factor,
- ii) a disease attributable to the degradation of at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1,
- iii) a disease attributable to a decrease in a gene product of a glucose metabolism-related gene,
- iv) a disease attributable to a decrease in a gene product of a gene on which at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1 acts as a transcription factor, and

- v) a disease attributable to a decrease in a gene product of the insulin gene and/or glucose transporter 2 gene.

136. (new) The agent according to claim 135, wherein the disease is diabetes.

137. (new) The agent according to claim 135, wherein the disease is liver adenoma or hepatocellular carcinoma, and the transcription factor of the glucose metabolism-related gene is hepatocyte nuclear factor 1  $\alpha$ .

138. (new) A method for identifying a compound that inhibits the degradation of a transcription factor of a glucose metabolism-related gene by calpain, wherein the method comprises contacting calpain and/or the transcription factor with a test compound under conditions that allow the cleavage of the transcription factor by calpain; and determining whether the test compound inhibits the cleavage by calpain of the transcription factor, by introducing a system using a signal and/or a marker capable of detecting the degradation of the transcription factor by calpain and detecting the presence, absence or change of the signal and/or the marker.

139. (new) The method according to claim 138, wherein the system using a signal and/or a marker capable of detecting the degradation of the transcription factor by calpain is a system using a signal and/or a marker capable of detecting the amount of the transcription factor or the amount of a degradation product of the transcription factor.

140. (new) The method according to claim 138, wherein the system using a signal and/or a marker capable of detecting the degradation of the transcription factor by calpain is a system using a signal and/or a marker capable of detecting the binding of calpain to the transcription factor.

141. (new) The method according to claim 138, wherein calpain is m-calpain or  $\mu$ -calpain.

142. (new) The method according to claim 138, wherein the transcription factor is at least one

member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1.

143. (new) A reagent kit containing at least one member selected from the group consisting of calpain, a polynucleotide encoding calpain, and a vector containing a polynucleotide encoding calpain; and at least one member selected from the group consisting of a transcription factor of a glucose metabolism-related gene that is degraded by calpain, a polynucleotide encoding the transcription factor, and a vector containing the polynucleotide.

144. (new) The reagent kit according to claim 143, wherein the transcription factor is at least one member selected from the group consisting of hepatocyte nuclear factor 4 $\alpha$ , hepatocyte nuclear factor 1 $\alpha$  and insulin promoter factor 1.

145. (new) The reagent kit according to claim 143, wherein calpain is m-calpain or  $\mu$ -calpain.